IV. REMARKS

Claim Status

Claims 10, 14-24 stand withdrawn from consideration as being drawn to a non-elected invention. Claims 2-4, 6, 9-12, 14-34, 36, 37 have been cancelled. Claims 41-46 are newly presented.

Specification

Applicants have clarified the passage in the specification by explaining that an error was made. The amendment filed 4/408 is objected to under 35 U.S.C. 1 32(a) because it introduces new matter into the disclosure. 35 U.S.C. 1 32(a) states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended page 3 to return it to its as filed state.

Claim Rejections - 35 USC § 112, first paragraph, Enablement

Claim 12 remains rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method to inhibit or prevent tumor growth by administration of a fibrin matrix.

Claim 12 has been cancelled.

Claim Rejections - 35 USC § 112, second paragraph, Indefinite

Claims 2-4, 6, 9, 11-13, 25-34, 36, 37 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject **matter** which applicant regards as the invention because they depend on a varying composition of fibrinogen variants as the starting material.

These claims have been cancelled and replaced by claims which do not recite the varying starting material, thus obviating this basis for rejection.

In addition the new claims specify that the percentages claimed are weight/weight percentages, thus obviating this ground of rejection.

Claim Rejections - 35 USC § 102

Claims 2-4, 6, 9, 25-34, 36, 37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Clark et al., USP 6,946,140. These claims have been replaced by claims 41-46.

New claims 41-43 are directed to a method comprising:

Modifying the angiogenesis properties of fibrin matrix by the process of

a) selecting a composition consisting of a specified amount of either high molecular weight or low molecular weight of fibrinogen, and

b) forming a fibrin matrix from the composition of step b).

New claims 44-46 are directed to modifying angiogenesis in a patient by administering a composition containing specified amounts HMW or LMW fibrinogen of fibrin matrix and forming a

fibrin matrix.

As stated by the examiner, Clark et al., US 6,946,140, discloses that the application of a fibrin clot to a wound enhances healing and fibroblast migration. The disclosure teaches fractionation of fibrinogen ppt. from normal plasma and produces fibrin gels from the various fractions and tests the gels for fibroblast migration activity. The fibrinogen is contacted with a wound surface.

Clark et al. is not interested in and does not recognize or disclose the relative proportions of the fibrinogen species in his precipitate.

As specifically noted by the examiner blood and plasma from different individuals have differing relative amounts of the various fibrinogen species. Thus, the amounts of the species as claimed by applicant may or may not be present in Clark et al.'s compositions.

The claims now specify that the percentage mentioned is a weight percentage and that it refers to the total fibrinogen amount in the composition. Indeed, from page 7, lines 22-35 of the specification, it should be clear for a person of skill in the art that the percentage is the weight percentage.

In the prior art cited by the examiner, fibrinogen compositions are used for achieving a fast closure of the wounds and the concentration of the fibrinogen solution used is rather high. These preparations are now commonly know as 'fibrin glue' and have a concentration of fibrin of about 20 mg/g.

When using the fibrinogen compositions for angiogenesis,

however, as disclosed in the present invention, it is counterproductive to have a fast clotting time, since this would counteract the formation of new blood vessels. Therefore, in the present invention, the fibrinogen composition is used with lower amounts of fibrinogen (see the Examples: 2 mg/g).

This is another difference of the presently claimed method with the prior art methods.

The angiogenetic effect of the fibrinogen appears to have a linear distribution with respect to the relative amount of HMW in the composition. In normal blood the percentage of HMW based on the total firbrinogen amount is about 70% w/w.

As disclosed in the specification, increases of the amount of HMW fibrinogen increases the angiogenetic properties of the compositions, while decreasing the relative amount of HMW decreases the angiogenetic properties.

However, with less than about 50% HMW there is no detectable angiogenesis. Thus, the HMW percentage must be at least about 50% w/w. Above this level, there is a linear relationship.

The discovery that this relationship exists was unknown to the art, is unexpected and forms the basis for the new use to which applicant disclosed.

It appears that two factors influence angiogenesis: the concentration of total fibrinogen (HMW + LMW), and, more importantly and forming the basis for this invention, the amount of HMW (or LMW) fibrinogen.

These are separate effects, and it is possible to modify angiogenesis at any concentration of (total) fibrinogen by changing the relative amounts of HMW or LMW fibrinogen. There are experimental data showing these results, and if deemed necessary by the examiner, applicant would contemplate filing a Declaration on these experiments.

As is clear from the Examples in the specification, a decrease in the amount of HMW to less than 50% at a concentration of 2 mg/g of total fibrinogen completely abolishes the angiogenetic activity. As indicated above, another factor influencing angiogenesis is the concentration of total fibrinogen.

It can be argued that the effect of decrease of angiogenesis by decreasing the relative amount of HMW fibrinogen can be compensated for by increasing the concentration of total fibrinogen thereby increasing the actual amount of HMW fibrinogen that is applied.

However, this would require that more total fibrinogen is applied and the total amount of fibrinogen influences the clotting time. The faster the clotting time, the more solid tissue is formed, and the more solid the tissue the harder it is to form blood vessels, i.e. to achieve angiogenesis.

Thus, changing the total concentration of fibrinogen would not be a suitable alternative to changing the relative concentration of HMW (or LMW) fibrinogen.

As stated by the examiner a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an

inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1 749 (Fed. Cir. 1991). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. See In re King, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986).

Thus, the doctrine of inherency does not require that the prior art recognize the components in the prior art composition as now claimed by applicant, but the doctrine is applicable only if applicants claimed composition is always present, not possibly present or present only in some instances.

Thus, Clark et al. does not disclose applicant's claimed compositions and applicant's claimed compositions are not inherent in Clark et al.'s disclosure.

Claim Rejections - 35 USC § 103

Cancelled claims 2-4, 6, 9-12, 14-34, 36, 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al., USP 6,946,140 in combination with Holm *et al.* or Hasegawa *et al.*, Smith *et al.* [V2] or Falls *et al.* or WO 00/62833.

New claims 41-43 are directed to a method comprising:

Modifying the angiogenesis properties of fibrin matrix by the process of

a) selecting a composition consisting of a specified amount of either high molecular weight or low molecular weight of fibrinogen, and

b) forming a fibrin matrix from the composition of step b).

New claims 44-46 are directed to modifying angiogenesis in a patient by administering a composition containing specified amounts HMW or LMW fibrinogen of fibrin matrix and forming a fibrin matrix.

As stated by the examiner:

1. US 6,946,140 discloses that the application of a fibrin clot to a wound enhances healing and fibroblast migration. The disclosure teaches fractionation of fibrinogen ppt. from normal plasma and produces fibrin gels from the various fractions and tests the gels for fibroblast migration activity.

2. WO 00/62833 discloses normal plasma which contains a mixture of fibrinogen types, precipitation by glycine, precipitation by ammonium sulfate 25% saturation which produces a purified fibrinogen with a mixture of types as evidence by fibrinogen bands I and II.

3. Holm *et al*. discloses a method comprising: selecting "normal" fibrinogen, fractionating to form fractions with more or less HMW, LMW and LMW' than the "normal" distribution (Fig 2), forming a fibrin matrix (clot) (page 1 71).

4. Hasegawa *et al*. disclose fractionating fibrinogen into fractions Fl and F2 with molecular weights of 340 and 325kDa (page 184), forming a fibrin clot (Fig. 2).

5. Smith *et al*. disclose producing mixtures of fibrinogen variants from purified variants (page 22081) and forming fibrin clots (Fig. 2).

6. Falls *et al.* disclose purifying fibrinogen to form fractions with different ratios of fibrinogen variants (p. 14252), forming fibrin clots.

The examiner states that substitution of the fibrin matrices of WO 00/62833 or Holm et al. or Hasegawa et al. or Smith et al. or Falls et al. for the fibrin matrices of US 6,946,140 in a method of treating patients with wounds would have been obvious because US '140 teaches the formation of fibrin matrices with different mixtures of fibrinogen variants and their application for enhancing wound healing.

The examiner notes that the specification does not contain any exemplification of wound treatment in a subject.

This is exactly the point applicant is advancing. Applicant does not disclose or claim a method of wound healing. The absence of any exemplification - as noted by the examiner - is clear evidence that something else is intended and is claimed. Basis for this claim appears at page 4, line 16 et seq. of applicant's specification.

The examiner concludes that, in the absence of evidence to the contrary, one of ordinary skill in the art may substitute any fibrinogen fraction in a fibrin clot for application to a wound and that one of ordinary skill in the art would have been motivated at the time of invention to produce this composition in order to obtain the results as suggested by the references with a reasonable expectation of success.

However, the results suggested by the references are not the results obtained by applicant. The art relates to wound healing and applicant's claims relate to something else - angiogenesis and the modification of angiogenesis.

Applicants have argued that US '140 does not reveal or even hint to the effects of fibrinogen composition on angiogenesis.

The examiner responds by stating that increased angiogenesis is merely the desired effect of the method of administering a fibrin clot (matrix) with an altered fibrinogen variant composition compared to a "normal" concentration and that therefore the method of administering the same product (with an altered variant content as compared to a "normal" variant content), would be reasonably expected to yield in the same result whether or not that result is overtly recognized. But although the prior art generically discloses mixtures with varying amounts of each component, it does not disclose the specific narrow range within which applicants product is efficacious.

This argument leads directly to the issue of inherency.

1. The Law

As stated by the examiner, to invalidate a patent by anticipation, a prior art reference normally needs to disclose each and every limitation of the claim. However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.

Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. However, the discovery of a previously unappreciated property of a prior art

composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

Thus, a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations.

The method of US '140 discloses various fibrinogen fractions and that fibrin matrix application to wounds enhances healing. In the absence of evidence concerning the differences between the cited prior art compositions and the lack of clarity of the composition of the claims, these are assumed to be the same compositions or obvious permutations of the compositions as presently administered in the claims.

An inherent feature need not be recognized at the time of the invention.

However, there are limitations imposed on the use of the doctrine. For example, the examiner must provide evidence showing inherency. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

In *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), the examiner's rejection was reversed because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art.

In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326

(CCPA 1981) stands for the proposition that, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' [emphasis supplied]

Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) stands for the proposition that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

When the prior art discloses a range which overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute."

What constitutes a "sufficient specificity" is fact dependent.

If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other

facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims or to render the claims unobvious. The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching.

2. Application of the Law to the Facts

The references disclose the use of mixtures of fibrinogen for wound healing. The proportions of the various types of fibrinogen disclosed by the references vary widely and may include the narrower ranges specified by applicant. The permissible ranges disclosed in the references are outside the range claimed by applicant or significantly broader than the range claimed by applicant. A major portion of the range disclosed by the prior art is inoperable in the process claimed by applicant.

The references do not recognize the necessity of using significantly lower concentrations of total fibrinogen or of utilizing HMW or LMW fibrinogen in the narrow range claimed by applicant or for the purposes claimed by applicant.

For all the foregoing reasons, applicant respectfully suggests the examiner has not made out a prima facie case of obviousness and favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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